I. AMENDMENTS

Please amend claim 31, line 4, by deleting ", in whole or in part,".

II. REMARKS

Claims 1 to 31 are currently pending in the subject application. The claims stand finally rejected under various provisions of 35 U.S.C. By this amendment, claim 31 has been amended to remove the phrase "in whole or in part." This amendment has been made to place the claims in condition for allowance or in better form for consideration on appeal. No new matter is introduced by this amendment and entry thereof is respectfully requested. In view of the preceding amendment and the following remarks, Applicants respectfully request the Examiner to reconsider and withdraw the rejections set forth in the Final Office Action.

35 U.S.C. § 112, First Paragraph

The Examiner maintained the rejection of claims 1 to 31 under 35 U.S.C. § 112, first paragraph, for allegedly not being enabled by the specification. In maintaining this rejection, the Examiner dismissed Applicants' prior remarks and reasserted her previous position with respect to the alleged failings of the specification.

In the prior Office Action, the specification was objected to for allegedly failing to adequately teach how to make and use the invention of claims 1 to 12 and 14 to 31 on several grounds. In one instance, the Examiner asserted that the specification allegedly fails to provide guidance regarding the routes of administration, amount, time course, and number of treatments, which the Examiner alleged are required to enable one of ordinary skill in the art to practice the claimed invention without undue experimentation. The Examiner also asserted that the relationship between HIV infection and macrophage depletion is not elucidated in the specification and that HIV infection in conjunction with Cl_2MDP treatment would appear to result in depletion, not prevention of depletion, of non-autologous hematopoietic cells.

Applicants respectfully traverse.

Independent claim 1 is directed to a method of preventing depletion in an animal of non-autologous hematopoietic cells comprising decreasing the number of endogenous macrophages to a level effective to substantially prevent depletion of the non-autologous hematopoietic cells. Claims 2 through 12 and 14 through 17 are variously dependent upon claim 1. Claim 18 is directed to a method of treating an immunocompromised animal comprising administering to the animal an effective amount of non-autologous hematopoietic cells and decreasing endogenous macrophages to a level sufficient to prevent substantial depletion of the non-autologous hematopoietic cells. Claim 19 is directed to a non-human animal comprising human hematopoietic cells wherein the mammal contains a decreased level of endogenous macrophages sufficient to prevent depletion of non-autologous hematopoietic cells. Claims 20 through 23 are variously dependent on claim 19.

Claim 24 is directed to a method of restoring hematopoietic cells to an immunocompromised human comprising the steps of administering an effective amount of human peripheral blood cells in conjunction with decreasing endogenous macrophages. Claims 26 through 30 are variously dependent upon claim 25. Claim 31 is directed to a method of improving engraftment efficiency for transplantation of a population of non-autologous hematopoietic stem cells in a host animal comprising the steps of ablating the endogenous stem cell population of the host animal and transplanting the stem cells into to the patient in conjunction with decreasing endogenous macrophages in the host animal.

All pending claims entail decreasing the number of endogenous macrophages to prevent depletion of non-autologous hematopoietic cells.

The Examiner's position is that all the teachings presented in the specification fail to provide the skilled artisan with the necessary guidance to make and use the inventions of the claims outlined above. The Examiner's one ground for rejection is that "the claims must be limited to a non-human animal since the specification fails to provide the guidance necessary to show the invention would work as claimed in humans." (Page 2 of the Office Action dated June 12, 1995). The Examiner's reasoned statement for rejecting the claims appeared to be a

utility rejection because it stated that the specification does not show that the invention would ***work*** in humans, even though it was raised under 35 U.S.C. § 112, first paragraph. Therefore, Applicants' attorney responded to the reason statement of the rejection, not its statutory classification. Nevertheless, the Examiner has refused to consider Applicants' position and respond accordingly. Even so, the specification enables the claimed inventions.

Applicants respectfully request that the Examiner remove the above ground for rejection of the claims against claims 13 and 19-24, which as filed are limited to non-human animals. With respect to the remaining claims, Applicants will direct their remarks to the patentability of the claims as far as they read on therapies for humans.

The law on enablement is set forth in the Manual of Patent Examining Procedures (MPEP):

> The enablement requirement refers to the requirement of 35 U.S.C. 112, first paragraph that the specification describe how to make and how to use the invention....
>
> The purpose of the requirement that the specification describe the invention in such terms that one skilled in the art can make and use the claimed invention is to ensure that the invention is communicated to the interested public in a meaningful way. The information contained in the disclosure of an application must be sufficient to inform those skilled in the relevant art how to both make and use the claimed invention. Detailed procedures for making and using the invention may not be necessary if the description of the invention itself is sufficient to permit those skilled in the art to make and use the invention....
>
> The test of enablement is whether one skilled in the art could make or use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation.... A patent need not teach and preferably omits what is well known in the art.... Determining enablement is a question of law based on underlying factual findings....
>
> The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation....
>
> The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, is it undue....

MPEP §§ 2164-2164.01 (citations omitted).

With this in mind, the specification must teach one of skill in the art how to decrease the number of endogenous macrophages in a human to a level effective to substantially prevent depletion of the non-autologous hematopoietic cells in the human to enable the embodiments of the claims currently rejected. Page 7, lines 7 through 19 of the specification states that endogenous macrophages can be depleted by treatment with L-leucine methyl ester, by the administration of colloidal carbon to the reticuloendothelial systems or by the administration of liposome-encapsulated Cl_2MDP. On page 10, line 3 through page 12, line 6, and Example 6 of the specification, Applicants teach that typically, Cl_2MDP is administered in a manner whereby it is taken up by macrophages but not other cells types, for example, by encapsulation in liposomes. How to make and use liposome-encapsulated Cl_2MDP is well known in the art at the time the invention was made as described in the specification and the Examiner's cited reference Pinto et al., (1991) *J. Leuk. Bio.* 49:579–586, and reference 33 cited therein. Example 6 of the application teaches that liposome-encapsulated drug administered intravenously will produce this effect. An effective amount is taught in the specification to be from 5 to 10 ml of liposomes per kg of human weight[1].

Therefore, Applicants have taught and enabled the route of administration (intravenously) and the amount (5 to 10 ml per kg of human weight). The specification further teaches that "an effective amount" can be empirically determined using monitoring methods well known to those of skill in the art (see page 11, line 12 to line 23 of the specification). Therefore, the number and time course of treatment can be easily determined by monitoring non-autologous macrophages using well known methods. Additionally, the specification provides examples of the number and

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[1] The Examiner incorrectly reads Applicants' statement regarding extrapolation from mice to humans. The specification recites that "[w]hile extrapolating to humans is not directly proportional, typically, the effective range would be 5 to 10 ml of these liposomes per kg of human weight." (Page 10, lines 24 to 27). Applicants do teach the effective range for human therapy, even though this range may not be directly proportional to the effective range when the invention is practiced in mice.

time course of treatments in Examples 7 through 9 of the application. Accordingly, the specification in combination with information known in the art, teaches how to make and use the invention as far as they read on human therapies.

The Examiner further asserted that the relationship between HIV infection and macrophage depletion is not elucidated. The Examiner has misunderstood the invention. The methods of this invention are particularly useful when the animal is immunocompromised (claims 7, 20 and 24). An animal may become immunocompromised due to radiation therapy (claim 10), chemotherapy (claim 11) or from infection with HIV (claims 8 and 25). Thus the relevant relationship is betweenHIV infection immunosuppression, not HIV infection and the number of macrophages.

In view of the preceding remarks, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 112, first paragraph.

35 U.S.C. § 112, Second Paragraph

The Examiner maintained the rejection of claims 1 to 23 under 35 U.S.C. § 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter of the invention. The Examiner opined that the terms "in whole or in part" and "substantially" are vague and unclear.

Without conceding the correctness of the Examiner's position, and merely to place the claim in condition for allowance, the phrase "in whole or in part" has been deleted from the claim. In view of the amendment to the claim, Applicants respectfully request that the rejection of claim 31 under 35 U.S.C. § 112, second paragraph, be removed.

However, Applicants maintain their position that the term "substantially" is definite to apprise those of skill in the art of the invention of the rejected claims.

It is well-settled law that the mere use of an adverb such as "substantially" will not render a claim indefinite and invalid for allegedly failing to meet the requirements of the second paragraph of 35 U.S.C. § 112 (*See, e.g., In re Mattison and Swanson*, 184 U.S.P.Q. 484, 486

(CCPA 1975)) (holding that the claim phrase "substantially increase" was not indefinite under § 112 and that an applicant's specification is not required to teach percentage of increase). Rather, claims using an adverb such as "substantial" are sufficiently definite if, when read in light of the specification, it will distinguish the claimed invention from the prior art and reasonably apprise those skilled in the art how to make and use the invention. *See, e.g. Rosemount, Inc. v. Beckman Instruments, Inc.*, 221 U.S.P.Q. 1 (Fed. Cir. 1988) (holding that one of skill in the relevant art would know what the claim term "substantially equal" delineates).

The definiteness requirement of § 112, second paragraph only requires that the claim be as precise in language as the relevant technology permits. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81 (Fed. Cir. 1986), *cert. denied,* 480 U.S. 947 (1987), wherein the Federal Circuit held that claim language describing antibodies having affinity of "at least about" 10^8 liters/mole was not indefinite because, read in light of the specification, a skilled artisan in the antibody field would be reasonably apprised of the claimed subject matter. The present invention is claimed as a method to "substantially" prevent depletion of non-autologous hematopoietic cells. The specification teaches various methods to perform the method and defines "substantial" on page 11, lines 3 to 11. Accordingly, claims 1 to 23 are not indefinite. Applicants request withdrawal of this rejection.

35 U.S.C. § 103

The Examiner maintained the rejection of claims 1 to 17 and 19 to 23 under 35 U.S.C. § 103 for allegedly being obvious in view of Aldrovandi et al. taken with Pinto et al.. Pinto et al. is cited for the teaching that Cl_2DMDP decreases the number of endogenous macrophages. The Examiner opined that the results of the decreased number of macrophages would be numerous in view of the major role of macrophages in maintaining the immune response. The Examiner remarked that although Applicants have argued that graft rejection and immunity to pathogens are disparate immune responses, knowing that the level of endogenous macrophages has been decreased, one of skill in the art would expect to see numerous responses and other macrophage-

related functions. Therefore, the Examiner remarked that Applicants' prior arguments regarding the nonobviousness of the combination were not found to be persuasive.

The traversal of the rejection is maintained.

Applicants have invented a method for preventing depletion of non-autologous hematopoietic cells as well as animal model system using this method. In one embodiment, the method entails decreasing the number of endogenous macrophages concomitant with the introduction of non-autologous hematopoietic cells. The invention stems from Applicants' novel finding that macrophages play an important role in the rapid clearance of non-autologous hematopoietic cells.

The claimed invention represents a significant advance in the ability to enhance and prolong circulation of non-autologous hematopoietic cells. Such an advance finds important applications in therapy as well as the study of hematopoietic, immunologic, and disease processes *in vivo*. This advance is embodied in the pending claims.

Claims 1 to 17 are directed to a method of preventing depletion in an animal of non-autologous hematopoietic cells comprising decreasing the number of endogenous macrophages to a level effective to substantially prevent depletion of the non-autologous hematopoietic cells. Claim 18 is directed to a method of treating an immunocompromised animal comprising administering to the animal an effective amount of non-autologous hematopoietic cells and decreasing endogenous macrophages to a level sufficient to prevent substantial depletion of the non-autologous hematopoietic cells. Claims 19 to 23 are directed to a non-human animal comprising human hematopoietic cells wherein the mammal contains a decreased level of endogenous macrophages sufficient to prevent depletion of non-autologous hematopoietic cells.

None of the cited prior art references, either alone or in combination, disclose or suggest the claimed inventions, all directed to a method of preventing depletion of non-autologous hematopoietic cells by decreasing the number of endogenous macrophages.

Aldrovandi et al. teach the use of the SCID-hu mouse as a possibly useful *in vivo* system for the study of HIV-1-induced pathology. Aldrovandi et al. perform experiments which involve

human fetal liver and thymus transplants which were later shown to be capable of being infected by HIV-1. Notably, Aldrovandi et al. also teach that human fetal Thy/Liv cells can be successfully transplanted in SCID mice. Aldrovandi et al. do not address or suggest the problem of rapid depletion of non-autologous hematopoietic cells; it does not discuss or suggest any relationship between a SCID-hu system and the problem of rapid depletion of non-autologous hematopoietic cells or a means to prevent it.

Pinto et al. describes the prominent role of macrophages in host resistance to pathogenic microorganisms. Applicants maintain their position that Pinto et al. merely disclose the effects of dichloromethylene diphosphonate (Cl_2MDP) encapsulated in liposomes on antimicrobial resistance, particularly against infection with *Listeria monocytogenes* and herpes simplex virus type 2. Pinto et al. does not address and therefore does not provide a solution to the problem of clearance of non-autologous hematopoietic cells.

However, the Examiner argued that because Cl_2MDP was found to decrease the number of endogenous macrophages and the results of a decreased number of macrophages would be expected to be numerous in view of the major role of macrophages in maintaining the immune response, the claimed invention is obvious. Applicants respectfully disagree.

While the role of macrophages in maintaining the immune response may be numerous, it was heretofore unknown that decreasing the number of macrophages would prevent depletion of non-autologous hematopoietic cells. The Examiner's position appears to be that one would expect this result without providing the requisite teaching or suggestion of such in the cited art. For this reason, Applicants submit that the references fail to teach or suggest the inventions of the claims because the art fails to teach or suggest the intellectual and technical leap as proffered by the Examiner in framing the rejection of the claims under 35 U.S.C. § 103. (*See In re Vaeck,* 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991) (The PTO was held to have erred in rejecting applicants' claims as *prima facie* obvious on the ground the prior art did not suggest the combination or convey to those of ordinary skill in the art a reasonable expectation of success at obtaining it.)

The Examiner assumes that because Cl_2MDP treatment resulted in macrophage depletion and immunosuppression which reduced resistance to two microbial agents, it would be known that reducing the number of endogenous macrophage would assist in preventing depletion of non-autologous hematopoietic cells. Applicants respectfully submit that none of the cited art teaches the relationship between reducing the number of endogenous macrophages and non-autologous hematopoietic cells and it cannot be assumed in framing a rejection under 35 U.S.C. § 103. As noted in *In re Spormann v. Heinke*, 150 U.S.P.Q. 449, 452 (CCPA 1966):

> "[T]he inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown."

The Examiner also relies on the teaching of Pinto et al. that administration of Cl_2MDP also causes an immunosuppression and that one of ordinary skill in the art would expected the transplanted cells to engraft since the immune system was suppressed. However, the Examiner has failed to recognize and appreciate a critical embodiment of the invention -- that reduction of the number of macrophages prevents depletion of non-autologous hematopoietic cells in the SCID-hu mouse -- an animal that inherently is immunosuppressed and therefore would not have graft versus host rejection.!!! Thus, one of skill in the art would not look to the teachings of Pinto et al. for providing the same or similar benefits in an animal that is immunosuppressed.

Indeed, when Applicants administered to 12 week old SCID mice an initial, primary, injection of Cl_2MDP with three subsequent injections (given every 5-7 days), the following results were obtained. Four days after the final injection, all treated mice and one group of 4 control, untreated mice received human PBLs. Two mice from each treatment group were then sacrificed 24 and 72 hours later for analysis. The results are shown in Figures 1 and 2. Human cells were detected at low levels in peripheral blood, spleen and bone marrow of non-treated SCID mice 24 hours after intravenous injection when assayed by FACS. However, the control mice were completely devoid of detectable cells in these tissues within 72 hours post-injection as demonstrated in Figure 1, control. In contrast, in the treated mice, human cells were detected at high levels under all titration conditions at both 24 and 72 hours in these tissues, as demonstrated

in Figure 1 (treatment 2). These results demonstrate that the depletion of the non-autologous hematopoietic cells are not the result of immunsuppression and therefore, the teaching of the prior art is not applicable to the claimed invention. More importantly, the Examiner's "reasoned statement" why the teachings of the prior art renders the claims obvious is not valid. Thus, the Examiner's statement appearing on page 6, i.e., that the role of macrophages in tissue rejection is old and well known in the art also does not provide a reasoned statement to reject the claims under 35 U.S.C. § 103, as the SCID-hu mouse is inherently without an endogenous immune system, which is why human thy/liv is suitable transplanted and maintained in the mouse.

Reconsideration and removal of this rejection is respectfully requested.

The Examiner also maintained the rejection of claim 18 under 35 U.S.C. § 103 for allegedly being unpatentable over Aldrovandi et al. and Pinto et al. as applied to claims 1 to 17 and 19 to 23 and further in view of Bernstein et al. The Examiner asserted that Bernstein et al. discloses that LPS upregulates HIV expression by macrophage growth factors. The Examiner asserted that however, in view of Bernstein's disclosure that macrophages are latent HIV reservoirs, it would have been obvious to the ordinary artisan to deplete macrophages in order to reduce the viral reservoirs.

Applicants maintain their traversal. Claim 18 is to a method of treating an immunocompromised animal which includes administering an effective amount of non-autologous hematopoietic cells and decreasing endogenous macrophages. Applicants reassert and incorporate by reference their position with respect to Aldrovandi et al. and Pinto et al. Aldrovandi et al. and Pinto et al., do not, either alone or in combination, disclose or suggest a method of treating an immunocompromised animal, or administering non-autologous hematopoietic cells in conjunction with decreasing endogenous macrophages. In addition, for the reasons provided above, there is no motivation to combine the references, and even if the references were combined, the references would not teach or suggest the invention. Pinto et al. disclosed that Cl_2MDP reduces microbial resistance in mice by reducing the number of

macrophages. In light of the failure of Aldrovandi et al. and Pinto et al. to render the claimed invention unpatentable, subsequent references cannot make up the deficiency.

Even if a combination of references based on the motivation to practice an invention other than, and unrelated to, the claimed invention were proper, the rationale given here is not even scientifically credible. Bernstein et al. disclose that activation of monocyte-derived macrophages with lipopolysaccharide (LPS) decreases HIV replication. Given this, the Examiner's statement that it would be obvious to "inactivate macrophages as a method of treatment in order to abolish viral replication" is without support. Moreover, Applicants' method is not a method of treating HIV infection, it is to treating an immunocompromised animal, the compromised state being the result of HIV infection. In view of the following remarks, reconsideration and withdrawal of this rejection are respectfully requested.

The rejection of claims 24 to 30 under 35 U.S.C. § 103 as allegedly unpatentable over Berenson and Baum taken with Pinto is maintained. The rejection of claim 31 as allegedly obvious over Baum et al. taken with Pinto et al. also is maintained.

Applicants reassert and incorporate by reference their position with respect to Pinto et al.

As noted above, the invention of the claims is not the result of immunosuppression. SCID-hu mice (inherently immunosuppressed) also showed depletion of administered PBLs 72 hours after administration. In contrast, treated SCID-hu mice showed a marked maintenance of non-autologous PBLs 72 hours after administration (see Figures 1 and 2). Therefore, the teaching of Pinto et al. regarding immunosuppression do not address or explain this result. The addition of Berenson et al. and Baum et al. do not overcome the deficiency present in Pinto et al. Accordingly, the combination of the references do not teach, suggest or enable the invention of claims 24 to 31. Reconsideration and withdrawal of the rejection of the claims as obvious over the cited art are respectfully requested.

III. CONCLUSION

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time. The Assistant Commissioner is authorized to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952 (Ref. No. 202962001300)**. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

If a telephone interview would advance prosecution and allowance of the pending claims, the Examiner is invited to telephone the undersigned at the number provided below.

Dated: June 25, 1996

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